

Remarks

The present claims are claims 16-31 and 33-37. Independent claims 16 and 33 as amended clarify that the sole preservative in the composition is the benzylauryldimethylammonium salt. Favorable reconsideration of this application is respectfully requested.

Initially, Applicants express their appreciation to Examiner Ghali for her courtesy in conducting the telephone discussion initiated by the undersigned on March 21, 2006. In the interview, Applicant proposed specifically defining in the claims that the compositions include a viscosity-increasing polymer. Applicant also pointed out the data in the specification at pages 6-8 regarding eye irritation. The Examiner pointed out she would prefer the term "consisting of". No specific agreement was reached.

Claims 16-39 were rejected under 35 USC 103 as unpatentable over Wong et al. (WO 94/15597) in view of Schoenwald et al. (US 4,271,143) further in view of Goldenberg et al. (WO 94/10976). Reconsideration is requested.

All the present claims define an ophthalmic composition, wherein irritation or damage to eye tissue is avoided even when the composition is applied repeatedly to eye tissue and/or resides on eye tissue for a lengthy period. As discussed in the present specification at pages 1 and 2, sterility of ophthalmic products applied to the eye is critical to avoid infection-producing microorganisms from contacting the eye. However, the preservatives also should not lead to irritation or damage to eye tissue. These requirements are especially important for ophthalmic compositions which must be used repeatedly over lengthy periods, or which have a prolonged residence time on the eye once applied.

The rejection of record stated that the avoidance of eye irritation or damage is intended use of the composition that does not impart patentability to the claims. However, this is a limitation of the claims, and it is respectfully submitted that, in compliance with Section 103(a), the prior art must disclose or suggest this limitation (which the prior art does not, as discussed for the individual references, below).

One known preservative for ophthalmic compositions is benzalkonium chloride (N-alkyl-N-benzyl-N,N-dimethyl-ammonium chloride) having a mixture of C<sub>8</sub>-C<sub>18</sub> alkyl radicals. As discussed in the present specification, benzalkonium chloride has excellent

antimicrobial properties, but in some subjects is poorly tolerated and may lead to irritation or even damage to the eye especially when used repeatedly or when applied for a prolonged residence time.

The present invention solves this invention by providing a preservative having excellent preservative properties but having reduced irritation potential, specifically, a benzylauryldimethylammonium salt, especially the chloride salt. These results are summarized at pages 6-8 of the specification, where ophthalmic compositions employing the benzylauryldimethylammonium salt were compared with control compositions employing either benzalkonium chloride or thimerosal (another known ophthalmic composition preservative). In contrast to the control compositions employing thimerosal and benzalkonium chloride, the compositions employing the benzylauryldimethylammonium salt, in accordance with the presently claimed invention, did not result in significant eye irritation and no tissue damage was observed.

As amended, all claims define that the preservative consists of the benzylauryldimethyl-ammonium salt.

Wong et al. discloses ophthalmic solutions comprising an acidic ophthalmic drug entity. Whereas benzylalkonium chloride is described as incompatible with such acidic drugs, due to the formation of insoluble ion-pair compounds which cause the solution to turn cloudy, lauralkonium chloride is described as compatible with such acidic ophthalmic drug entities due to no apparent formation of such insoluble ion-pair compounds. Wong et al. does not disclose compositions having a vehicle with increased viscosity, such that the compositions have longer residence time on the eye, and Wong et al. does not describe or suggest in any manner the avoidance of irritation or damage to eye tissue when an ophthalmic composition is applied repeatedly to eye tissue and/or resides on eye tissue for a lengthy period. Accordingly, Wong et al. does not recognize the problem solved by the present invention, nor suggest any solution to this problem.

Schoenwald et al. discloses an aqueous dispersion of an ophthalmic drug and a high molecular weight polymer which forms a highly viscous gel. Schoenwald et al. does not disclose benzylauryldimethylammonium salts. In fact, Schoenwald et al. employs benzalkonium chloride as a preservative; see, for example, Examples I and II. Thus,

Schoenwald et al. is no more relevant than the control compositions disclosed in the present specification.

Goldenberg et al. discloses aqueous polyvinyl alcohol/borate buffer drug delivery systems that are liquid at low pH values and gels when pH is raised to over 7. Goldenberg et al. does not disclose benzylauryldimethylammonium salts. In fact, Goldenberg et al. describes benzalkonium chloride and thimerosal, among others, as suitable preservatives; see, for example, page 5, second full paragraph. Thus, Goldenberg et al. is no more relevant than the control compositions disclosed in the present specification.

In summary, the cited references, individually or combined, do not disclose or suggest the use of benzylauryldimethylammonium salts to preserve ophthalmic compositions while avoiding irritation or damage to eye tissue when the compositions are applied repeatedly to eye tissue and/or resides on eye tissue for a lengthy period. Accordingly, it is respectfully submitted no *prima facie* case of obviousness has been established. Further, the fact that no reference recognizes the problem solved by the presently claimed invention is evidence of nonobviousness. Schoenwald et al. and Goldenberg et al., in essence, suggest there is no problem with using benzalkonium chloride or thimerosal as a preservative in ophthalmic compositions having prolonged residence time on the eye. Wong et al. merely discloses using lauralkonium chloride in liquid ophthalmic compositions when there is an issue with compatibility of the preservative with acidic ophthalmic drug entities.

A favorable action in the form of a Notice of Allowance is respectfully requested. The Examiner is invited to contact the undersigned to resolve any remaining issues.

Respectfully submitted,



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